```
=> file .meeting
'EVENTLINE' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):ignore
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                      0.21       0.21

FILE 'AGRICOLA' ENTERED AT 15:01:01 ON 19 MAY 2004

FILE 'BIOTECHNO' ENTERED AT 15:01:01 ON 19 MAY 2004
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=> c peptide
L1          192 FILE AGRICOLA
L2         1090 FILE BIOTECHNO
L3          109 FILE CONFSCI
L4            6 FILE HEALSAFE
L5            0 FILE IMSDRUGCONF
L6          553 FILE LIFESCI
L7            2 FILE MEDICONF
L8         2415 FILE PASCAL

TOTAL FOR ALL FILES
L9         4367 C PEPTIDE

=> (C peptide)(P)insulin(P)tracer
L10           1 FILE AGRICOLA
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'PEPTIDE)(P)INSULIN'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN(P)TRACER'
L11          18 FILE BIOTECHNO
L12           0 FILE CONFSCI
L13           0 FILE HEALSAFE
L14           0 FILE IMSDRUGCONF
L15           0 FILE LIFESCI
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
```

FIELD CODE - 'AND' OPERATOR ASSUMED 'PEPTIDE)(P)INSULIN'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN(P)TRACER'
L16 0 FILE MEDICONF
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'PEPTIDE)(P)INSULIN'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN(P)TRACER'
L17 5 FILE PASCAL

TOTAL FOR ALL FILES
L18 24 (C PEPTIDE)(P) INSULIN(P) TRACER

=> l18 and (second antibody)
L19 0 FILE AGRICOLA
L20 1 FILE BIOTECHNO
L21 0 FILE CONFSCI
L22 0 FILE HEALSAFE
L23 0 FILE IMSDRUGCONF
L24 0 FILE LIFESCI
L25 0 FILE MEDICONF
L26 0 FILE PASCAL

TOTAL FOR ALL FILES
L27 1 L18 AND (SECOND ANTIBODY)

=> d l27 ibib abs total

L27 ANSWER 1 OF 1 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1992:22261914 BIOTECHNO
TITLE: A rapid and sensitive radioimmunoassay for the measurement of proinsulin in human serum
AUTHOR: Bowsher R.R.; Wolny J.D.; Frank B.H.
CORPORATE SOURCE: Lilly Clinical Research Laboratory, Wishard Memorial Hospital, 1001 West Tenth Street,Indianapolis, IN 46202, United States.
SOURCE: Diabetes, (1992), 41/9 (1084-1090)
CODEN: DIAEAZ ISSN: 0012-1797
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1992:22261914 BIOTECHNO
AB RIA methodology is used widely to measure proinsulin in human serum. However, some RIAs lack the sensitivity necessary to quantify proinsulin in unextracted serum and require long incubation periods. We developed an RIA with a sensitivity of 3.5 pM that permits the routine measurement of proinsulin in <48 h. This was accomplished by using a nonequilibrium binding reaction at room temperature and PEG-assisted **second antibody** precipitation as the method for separating bound and free proinsulin. We obtained a specific antiproinsulin antibody by adsorbing the initial goat antiserum with human **C-peptide**-agarose. Proinsulin produced 50% displacement of **tracer** at 25.6 pM, whereas both human **insulin** and **C-peptide** failed to displace **tracer** at concentrations as high as 1 μM. We evaluated several cleaved derivatives of proinsulin for cross-reactivity with the antibody. B-chain-**C-peptide** cleaved derivatives (<=50% cross-reactivity) were more potent than A-chain-**C-peptide** cleaved derivatives (<5% cross-reactivity). However, all derivatives cleaved in the region from 56-60 failed to cross-react with the antiserum. These data indicate that a major antigenic determinant is present on the **C- peptide** region of proinsulin adjacent to the A-chain-**C-peptide** junction. After

administration of an oral glycemic challenge, the mean fasting serum concentration of proinsulin in normal adults rose from 4.1 ± 0.28 to 23.6 ± 3.8 pM. We found a significant difference in the proinsulin concentrations in 6 adults before and after a glycemic challenge when two different antibodies were used in the RIA. Based on the antibodies different specificity for proinsulin, we concluded that B-chain-**C** -**peptide** junctional split forms of proinsulin comprise a significant portion of circulating proinsulin material after a glycemic challenge.

```
=> file .chemistry
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       8.48       8.69

FILE 'CAPLUS' ENTERED AT 15:04:02 ON 19 MAY 2004
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FILE 'USPATFULL' ENTERED AT 15:04:02 ON 19 MAY 2004
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=> (c peptide)(P)insulin(P)tracer(P)(second antibody)
L28           2 FILE CAPLUS
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'PEPTIDE)(P)INSULIN'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN(P)TRACER'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'TRACER(P)(SECOND'
L29           1 FILE BIOTECHNO
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'PEPTIDE)(P)INSULIN'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN(P)TRACER'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'TRACER(P)(SECOND'
L30           0 FILE COMPENDEX
L31           0 FILE ANABSTR
L32           0 FILE CERAB
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'PEPTIDE)(P)INSULIN'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN(P)TRACER'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
```

FIELD CODE - 'AND' OPERATOR ASSUMED 'TRACER(P)(SECOND'
L33 0 FILE METADEX
L34 0 FILE USPATFULL

TOTAL FOR ALL FILES
L35 3 (C PEPTIDE)(P) INSULIN(P) TRACER(P)(SECOND ANTIBODY)

=> dup rem'
ENTER REMOVE, IDENTIFY, ONLY, OR (?):remove
ENTER L# LIST OR (END):l35
'REM'' IS NOT VALID. VALID FILE NAMES ARE 'CAPLUS, BIOTECHNO'
You have entered a file name of duplicates to keep that is not
referenced by any of the L#s specified for this DUPLICATE command.
The file names of duplicates that can be kept are listed above.
Please enter one of these file names.

=> d l35 ibib abs total

L35 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:320215 CAPLUS
DOCUMENT NUMBER: 134:339540
TITLE: A new immunologic assay to determine C-peptide containing impurities in samples of human insulin and derivatives thereof
INVENTOR(S): Gerl, Martin; Steinert, Cornelia
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001031336 | A2 | 20010503 | WO 2000-EP10482 | 20001025 |
| WO 2001031336 | A3 | 20011108 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1228374 | A2 | 20020807 | EP 2000-974449 | 20001025 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| JP 2003513243 | T2 | 20030408 | JP 2001-533423 | 20001025 |

PRIORITY APPLN. INFO.: DE 1999-19951684 A 19991027
WO 2000-EP10482 W 20001025

AB The invention relates to a process for detecting or determining a **C-peptide**-containing impurity in a sample of recombinantly produced human **insulin** or a derivative thereof, by a non-radioactive assay, comprising the steps: (a) preparing a sample of recombinantly produced human **insulin** or a derivative thereof; (b) mixing the samples with dilution buffer; (c) adding a **tracer** to mixture (b); (d) adding antibody specific for the **C-peptide** impurity to mixture (c); (e) adding "**C-peptide second antibody** bead" having at least one label to mixture (d); and (f) detecting or determining the presence of the **C-peptide**-containing impurity.

L35 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:564015 CAPLUS
DOCUMENT NUMBER: 117:164015
TITLE: A rapid and sensitive radioimmunoassay for the measurement of proinsulin in human serum
AUTHOR(S): Bowsher, Ronald R.; Wolny, James D.; Frank, Bruce H.
CORPORATE SOURCE: Dep. Drug Disposit. Bioanal. Res., Eli Lilly and Co., IN, USA
SOURCE: Diabetes (1992), 41(9), 1084-90
CODEN: DIAEAZ; ISSN: 0012-1797
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although RIA methodol. is used widely to measure proinsulin in human serum, some RIAs lack the sensitivity necessary to quantify proinsulin in unextd. serum and require long incubation periods. An RIA with a sensitivity of 3.5 pM was developed which permits the routine measurement of proinsulin in <48 h. This was accomplished by using a nonequil. binding reaction at room temperature and PEG-assisted **second antibody** precipitation as the method for separating bound and free proinsulin. A specific anti-proinsulin antibody was obtained by adsorbing the initial goat antiserum with human **C-peptide**-agarose. Proinsulin produced 50% displacement of **tracer** at 25.6 pM, whereas both human **insulin** and **C-peptide** failed to displace **tracer** at concns. as high as 1 μM. Several cleaved derivs. of proinsulin were evaluated for cross-reactivity with the antibody. B-chain-**C-peptide** cleaved derivs. (≤50% cross-reactivity) were more potent than A-chain- **C-peptide** cleaved derivs. (<5% cross-reactivity). However, all derivs. cleaved in the region from 56-60 failed to cross-react with the antiserum. These data indicate that a major antigenic determinant is present on the **C-peptide** region of proinsulin adjacent to the A-chain-**C-peptide** junction. After administration of an oral glycemic challenge, the mean fasting serum concentration of proinsulin in normal adults rose from 4.1 to 23.6 pM. Differences in the proinsulin concns. in 6 adults before and after a glycemic challenge were found when 2 different antibodies were used in the RIA. Based on the antibodies different specificities for proinsulin, B-chain-**C-peptide** junctional split forms of proinsulin material apparently comprise a significant portion of circulating proinsulin material after a glycemic challenge.

L35 ANSWER 3 OF 3 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1992:22261914 BIOTECHNO
TITLE: A rapid and sensitive radioimmunoassay for the measurement of proinsulin in human serum
AUTHOR: Bowsher R.R.; Wolny J.D.; Frank B.H.
CORPORATE SOURCE: Lilly Clinical Research Laboratory, Wishard Memorial Hospital, 1001 West Tenth Street,Indianapolis, IN 46202, United States.
SOURCE: Diabetes, (1992), 41/9 (1084-1090)
CODEN: DIAEAZ ISSN: 0012-1797
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
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